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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/389,545	09/03/99	DUNSTAN C	A-605

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EXAMINER	
TEDESCHI, B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 03/14/01

Please find below and/or attached an Office communication concerning this application r proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/389,545	DUNSTAN, COLIN R.	
	Examiner	Art Unit	
	Bruce W. Tedeschi	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) 2,17-20 and 22 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,3-16,21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

This application was filed on September 3, 1999. A preliminary amendment was received and entered on January 21, 2000.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1, 3-21, drawn to Method for treating Lytic Bone Disease, classified in class 424, subclass 572.

II. Claims 2, 4-12, 15-21, drawn to Method for treating/preventing Cancer Metastasis, classified in class 424, subclass 572.

III. Claim 22, drawn to Method for treating/preventing Myeloma, classified in class 424, subclass 572.

Inventions I, II, and III are related as process of use of OPG polypeptide. In the instant case, the processes described [lytic bone disease, metastasis, and myeloma] are considered to be three separate medical conditions. Lytic bone disease refers to a condition characterized by the loss of bone tissue, metastasis refers to the movement of tumor cells from primary to secondary sites, and myeloma refers to a condition characterized by the overproliferation of hematopoietic precursors. Each condition has a different constellation of symptoms and etiology. Therefore, a prior art search for treatments relating to any one individual condition would not elicit prior art in the other two conditions. Consequently, the search and examination burden for the three independent methods would place an undue burden on the examiner.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

This application contains claims directed to the following species falling within a Group of claims:

Group I

Species A – Radiation

Species B – Chemotherapy

Species C – Antibodies

Species D – Non-antibody polypeptides

Group II

Species A – Radiation

Species B – Chemotherapy

Species C – Antibodies

Species D – Non-antibody polypeptides

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1,2,3,4 and 15 are generic. Each species are distinct from each other because they refer to a different product or process. Species A and B refer to methods of cancer treatment but species A involves the utilization of electromagnetic energy while species B involves the utilization of drugs which usually impede cellular mitosis. Species C and D represent products but species

C refers to a specific kind of protein that binds antigens while species D refers to the heterogeneic constellation of all other proteins (e.g. growth factors, enzymes, structural proteins, etc.). Therefore, a prior art search for any one of the species would not elicit prior art in the other species. Consequently, the search and examination for the four species would place an undue burden on the examiner

Because these species are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, an election of species for examination purposes as indicated is proper.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Robert B. Winter on 11/13/00 a provisional election was made with traverse to prosecute the invention of I [Method for Treating Lytic Bone Disease] with election of Species B, Chemotherapy [claims 1, 3-16, 21] .

Affirmation of this election must be made by applicant in replying to this Office action. Claims 2, 17-20, 22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

The disclosure is objected to because of the following informalities:

The specification contains sequence disclosures without corresponding SEQ. ID. Nos. on Page 16. Sequence compliance is required for any amino acid of 4 or more residues as defined in 37 CFR 1.821 and MPEP2421.02. Correction is requested.

The reference to a co-pending patent application on Page 45 has two blank spaces. Correction is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-7, 12-16, and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting bone loss by administering FcΔC-OPG [22-194], does not reasonably provide enablement for prevention of lytic bone disease or inhibition/treatment of bone loss using unfused OPG or any of its fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Many factors are considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction or guidance provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Claims 1, 3-7, 12-16, and 21 are drawn to a method of preventing or treating lytic bone disease comprising administering a therapeutically effective amount of an unfused OPG polypeptide or any of its fragments.

Claims 1, 3-7, 12-16, and 21 are not enabling for the following reasons: (1) the specification discloses, and the prior art teaches, no working examples of unfused OPG in treating bone loss or preventing bone disease; (2) the specification provides no direction to enable the invention using unfused OPG; (3) the specification provides no guidance as to how OPG administration should be used as a preventive treatment; and (3) the level of predictability is low. Predictability is low because treatment or prevention of disease with unmodified proteins is subject to multi-factorial problems, given the current state of the art. For example, Sternson (New York Academy of Sciences, 207:19-21, especially page 19, paragraph 3) teaches that there are significant obstacles to protein delivery by any route of administration and these obstacles include chemical/physical instability, enzymatic breakdown, potential for eliciting an

immunogenic response, and inability to be efficiently transported suitable to support therapeutic needs. In regard to claims drawn to the use of unfused OPG or its fragments, applicant discloses that only an OPG fused with an Fc region of an Ig molecule offers significant advantages over unfused OPG (Page 8, lines 3-16 and Page 12, lines 6-9). In light of Sternson's teachings, the applicant has not provided any convincing evidence that unfused OPG would overcome these obstacles. In regard to claims drawn to the use of OPG as a preventative therapy for lytic bone disease, the specification provides no guidance as to how OPG administration should be appropriately timed when used as a preventative composition, since a patient would ordinarily have no idea that he has lytic bone disease, until after-the-fact. The applicants disclosed a method of preventing bone loss due to metastasis by treating animals with a fused OPG composition prior to injection of cancer cells. However, in humans, tumors are significantly progressed before they become discernible. (Lodish et al. Molecular Cell Biology, 4th edition, page 1055, column 1, paragraph 3). Thus, OPG could only realistically be used to treat, not prevent, bone loss due to metastasis.

In the absence of working examples and further guidance from the applicants as to how unfused OPG could be used to prevent bone disease and in view of the unpredictability of therapies based on unmodified proteinaceous compositions, one skilled in the art would be forced into undue experimentation to practice the invention as claimed. The claims are rejected.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-16 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As regards to claims 1, 4-16 and 21, the claims are drawn to prevention or treatment of "lytic bone disease".

It is not clear from the disclosure of the specification or the teaching of the prior art, which bone loss disturbances can be defined by the term "lytic bone disease". The prior art does not teach the criteria under which bone pathology would qualify as lytic bone disease. It is known that not all bone losses have the same etiology or disease mechanisms. For example, Paget's disease, appears to have a slow viral infection etiology (Harvey et al.,1982, J Clin Pathol 35:771-9, Page 774, Figure 4) while there is no evidence for a viral etiology underlying myeloma or hyperparathyroidism. Also, the mechanisms of bone loss are not identical between various bone loss disturbances. For example, the nature of the bone resorbing surface in lymphoid malignancy is different from that in hyperparathyroidism (Mundy, 1991, Bone 12 Suppl 1 S1-6, Page S4, 1st column, paragraph 3). Since neither the specification nor the claims distinctly points out the metes and bounds of this term, the claims are rejected.

As regards to claims 3-16 and 21, the claims are drawn to prevention or treatment of "osteosclerotic bone metastasis". It is not clear from the specification

whether the claim is drawn to a therapeutic invention directed to the loss of bone or a therapeutic invention directed to metastasis.

Claims 15 and 16 are indefinite because: (1) Claim 15 recites the limitation "cancer therapy agent" in line 33 and (2) claim 16 incorporates the limitation by reference. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,3, 5, and 8-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyle et al. (Patent # WO 97/23614).

Claims 1, 3, 5, and 8-16 are drawn to a method of treating lytic bone disease or osteosclerotic bone metastasis comprising administering a therapeutically effective amount of OPG polypeptide, OPG fragment, or modified OPG.

Boyle et al. teach the treatment of bone disorders, including osteolytic metastasis, comprising administering a therapeutically effective amount of a modified or unmodified OPG polypeptide, OPG fragment, or modified OPG (Page 24, lines 7-29; Page 36, lines 21-25; and Page 37, line 27). Since all limitations of the claims are anticipated by Boyle et al., the claims are rejected.

Claims 1, 5, 8-10, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Simonet et al. (Cell, 1997, 89:309-19).

In regard to claims 1, 5, and 8-10, the claims are drawn to the treatment or prevention of lytic bone disease by a composition, at any therapeutically effective amount, comprising any OPG or a truncated portion of OPG, OPG fragments (residues 186-401 or 22-194), or OPG fusion polypeptide with Fc region fused to residues 22-194.

Simonet et al. teach the effective treatment of ovariectomy-induced bone loss by a composition consisting of OPG fusion polypeptide with Fc region fused to residues 22-401 (Figure 7 and legend at Page 316). Since all limitations of the claims are anticipated by Simonet et al., the claims are rejected.

In regard to claim 21, the claim is drawn to a therapeutically effective amount of an OPG polypeptide or an OPG fusion polypeptide between 0.1 mg/kg and 10 mg/kg.

Simonet et al. teach the effective treatment of ovariectomy-induced bone loss by a composition consisting of OPG fusion polypeptide with Fc region fused to residues 22-401 at a concentration of 10 mg/kg (Page 318, column 1, 3rd paragraph). Since all limitations of the claim is anticipated by Simonet et al., the claim is rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3-16, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyle et al. in view of Conte et al. (Annals of Oncology 5:S41-S44, 1994).

Claims 1, 3-16, and 21 are drawn to a method of treating lytic bone disease or osteosclerotic bone metastasis comprising administering a therapeutically effective amount of OPG polypeptide alone, or in conjunction with a cancer therapy agent.

Boyle et al. teach the inhibition of bone resorption using a therapeutically effective amount of a modified or unmodified OPG polypeptide (Page 36, lines 21-25 and Page 37, line 27). Boyle et al. differs do not teach the inhibition of bone resorption using OPG in conjunction with a cancer therapy agent.

Conte et al. teach the use of a composition, pamidronate, to inhibit bone resorption as part of a simultaneous treatment regime with chemotherapy in breast cancer patients (Page S41, 1st column, last paragraph).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to treat cancer patients that are exhibiting bone loss

with OPG to directly inhibit osteoclasts, as taught by Boyle et al., and to simultaneously treat the cancer as commonly done in the art as taught by Conte el al. Since the majority of patients with certain types of cancer (e.g. breast cancer) develop lytic bone metastases (Conte et al., Page 43, 1st column, paragraph 4), one would be motivated to combine chemotherapy with OPG in order to obtain the obvious advantages of inhibition of bone loss with inhibition of the cancer metastases as taught by Conte et al.

Claims 3, 4, 6-7, 11-16, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simonet et al. in view of Conte et al. (Annals of Oncology 5:S41-S44, 1994).

Claims 3, 4, 6-7, 11-16, and 21 are drawn to a method of treating osteosclerotic bone metastasis comprising administering a therapeutically effective amount of a modified or unmodified OPG polypeptide, alone or in conjunction with a cancer therapy agent. Simonet et al. teach the treatment of such osteopenic disorders as osteolytic metastases using OPG alone (page 317, column 1, paragraph 2). Simonet et al. do not teach the treatment of osteolytic metastases using OPG in conjunction with a cancer therapy agent.

Conte et al teach the use of a bone loss-inhibiting composition in conjunction with chemotherapy in breast cancer patients (Page S41, 1st column, last paragraph).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to treat cancer patients that are exhibiting bone loss with OPG to directly inhibit osteoclasts, as taught by Boyle et al., and to simultaneously treat the cancer as commonly done in the art as taught by Conte el al. Since the

majority of patients with certain types of cancer (e.g. breast cancer) develop lytic bone metastases (Conte et al., Page 43, 1st column, paragraph 4), one would be motivated to combine chemotherapy with OPG in order to obtain the obvious advantages of inhibition of bone loss with inhibition of the cancer metastases as taught by Conte et al.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce W. Tedeschi whose telephone number is 703-306-4823. The examiner can normally be reached on Monday - Friday, 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-3014 for regular communications and 703-308-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Bruce W. Tedeschi, PhD
March 12, 2001

YVONNE EYLER, PH.D
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